Research, Society and Development, v. 10, n. 12, e264101220410, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i12.20410

Use of antimicrobials in patients with COVID-19 without prior evaluation of an associated bacterial infection

Uso de antimicrobianos em pacientes com COVID-19 sem avaliação prévia de uma infecção bacteriana associada

Uso de antimicrobianos en pacientes com COVID-19 sin evaluacíon previa de una infeccíon bacteriana asociada

Received: 09/09/2021 | Reviewed: 09/15/2021 | Accept: 09/18/2021| Published: 09/19/2021

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Abstract

This paper aims to clarify and present discussions about the COVID-19 disease, its variants and prevention measures, as well as clarifying the excessive use of antimicrobials in the protocols of patients infected with it, as this practice can intensify an already existing public health problem, which is antimicrobial resistance. The methodology used in this research was a literature review on bacterial resistance due to the indiscriminate use of antimicrobials and the possible impacts caused in the COVID-19 pandemic, as well as the variants of worldwide concern, based on the Scientific Electronic Library Online databases - SCIELO, National Library of Medicine - PubMed, CAPES Journal Portal, Academic Google and National Health Surveillance Agency (ANVISA). Based on the literature presented here, it is concluded that COVID-19 is a disease caused by the acute respiratory syndrome (SARS-CoV-2) presenting a clinical spectrum ranging from asymptomatic infections to severe conditions. Several variants have emerged in several countries modifying the dynamics of transmissibility and potential immune flight from the disease, the Delta variant (B.1.617.2) being a greater threat to public health due to its high transmissibility. The misuse and excessive use of antimicrobials prescribed for the treatment of this disease can favor the emergence of superbugs and such resistance is a global problem. Therefore, the help of laboratory and clinical tests is essential to carry out a therapeutic intervention, observing the best options for each clinical case, since COVID-19 is a new disease and still under study.

Keywords: SARS-CoV-2 infection; Anti-infective agents; Drug resistance bacterial.

Resumo

Este trabalho tem como objetivo esclarecer e apresentar discussões sobre a doença COVID-19, suas variantes e medidas de prevenção, bem como esclarecer quanto ao uso excessivo de antimicrobianos, nos protocolos de pacientes

infectados pela mesma, uma vez que esta prática pode intensificar um problema de saúde pública, já existente, que é a resistência a antimicrobianos. A metodologia utilizada nesta pesquisa foi uma revisão de literatura sobre a resistência bacteriana pelo uso indiscriminado de antimicrobianos e os possíveis impactos causados na pandemia de COVID-19, bem como as variantes de preocupação mundial, baseou-se nos bancos de dados *Scientific Electronic Library Online* - SCIELO, *National Library of Medicine* - PubMed, Portal de Periódicos CAPES, Google Acadêmico e Agência Nacional de Vigilância Sanitária (ANVISA). Embasado na literatura aqui apresentada, conclui-se que A COVID-19 é uma doença causada pela síndrome respiratória aguda (SARS-CoV-2) apresentando um espectro clínico variando de infecções assintomáticas a quadro graves. Diversas variantes surgiram em vários países modificando a dinâmica de transmissibilidade e de potencial fuga imunitária da doença, sendo a variante Delta (B.1.617.2) uma ameaça maior à saúde pública devido sua alta transmissibilidade. O uso indevido e excessivo dos antimicrobianos prescritos no tratamento desta doença pode favorecer o surgimento de superbactérias e tal resistência é um problema global. Sendo assim, o auxílio de exames laboratoriais e clínicos é fundamental para fazer uma intervenção terapêutica observando as melhores opções para cada um dos casos clínicos, uma vez que a COVID-19 é uma doença nova e ainda em estudo.
Palavras-chave: Infecção por SARS-CoV-2; Agente antimicrobiano; Farmacorresistência bacteriana.

Resumen

Este trabajo tiene como objetivo aclarar y presentar discusiones sobre la enfermedad COVID-19, sus variantes y medidas de prevención, así como aclarar el uso excesivo de antimicrobianos en los protocolos de los pacientes infectados por ella, ya que esta práctica puede intensificar un problema de salud pública ya existente, que es la resistencia a los antimicrobianos. La metodología utilizada en esta investigación fue una revisión de la literatura sobre la resistencia bacteriana por el uso indiscriminado de antimicrobianos y los posibles impactos causados en la pandemia de COVID-19, así como las variantes de preocupación mundial, a partir de las bases de datos *Scientific Electronic Library Online* - SCIELO, *National Library of Medicine* - PubMed, Portal de Periódicos CAPES, Google Académico y Agencia Nacional de Vigilancia Sanitaria (ANVISA). Basándonos en la literatura presentada, concluimos que la COVID-19 es una enfermedad causada por el síndrome respiratorio agudo (SARS-CoV-2), con un espectro clínico que va desde las infecciones asintomáticas hasta los casos graves. Han surgido diversas variantes en varios países, cambiando la dinámica de la transmisibilidad y el potencial escape inmunológico de la enfermedad, siendo la variante Delta (B.1.617.2) una de las principales amenazas para la salud pública debido a su alta transmisibilidad. El uso inapropiado y excesivo de los antimicrobianos prescritos en el tratamiento de esta enfermedad puede favorecer la aparición de superbacterias y dicha resistencia es un problema mundial. Por lo tanto, la ayuda de los exámenes de laboratorio y clínicos es fundamental para realizar una intervención terapéutica observando las mejores opciones para cada caso clínico, ya que la COVID-19 es una nueva enfermedad aún en estudio.
Palabras clave: Infeccíon por SARS-CoV-2; Agente antimicrobiano; Farmacorresistencia bacteriana.

1. Introduction

In recent years, due to technological advances, access to the most diverse information on search sites, as well as discussions in virtual communities, has become fast and independent. This advance also promoted the growth of the indiscriminate and improper use of medicines without a medical prescription. According to Souza et al., 2008, self-medication can result in undesirable effects, ranging from the masking of evolving diseases to the emergence of iatrogenic diseases, that is, a disease state, adverse effects or complications caused or resulting from medical treatment (Ferraz et al., 1982; Souza et al., 2008).

According to Teixeira (2019), in Brazil, the sale of antimicrobials exceeds that of analgesics and antipyretics. The inappropriate use of these drugs can accelerate the bacteria's defense mechanisms, causing a certain type of antimicrobial to progressively lose its effectiveness (Teixeira, 2019). In addition, there is still the ingestion of antimicrobials from animal foods, which are treated with these drugs, with large amounts of them (Luiz et al., 2018; Miranda et al., 2018; Pereira et al., 2020).

Antimicrobial agents have different behaviors, acting as a bactericide, causing the death of microorganisms responsible for the infectious process. This group includes several drugs, such as: beta-lactams, aminoglycosides, rifampicin, vancomycin, quinolone, among others. While those with bacteriostatic actions, which inhibit bacterial growth, even though the microorganism remains viable, are: tetracyclines, chloramphenicol, macrolides, sulfamides, among others (Luiz, 2019; Oliveira Junior, 2016).

It should be remembered that the same antimicrobial can show a different activity against different microorganisms, including the antimicrobial activity can be different in a microorganism located in different geographic areas. Thus, the concept of antimicrobial activity requires standardization or quantification that is achieved through in vitro assays (antibiogram, dilution techniques and molecular biology) to prove the microorganism's susceptibility to the antimicrobial (Oliveira Junior, 2016).

According to the Ministry of Health (MS), COVID-19 is a disease caused by the coronavirus, called SARS-CoV-2, which has a clinical spectrum ranging from asymptomatic infections to severe conditions. According to the World Health Organization (WHO), about 80% of patients with COVID-19 may be asymptomatic or oligosymptomatic, while the remaining 20% of detected cases require hospital care. It is observed that in some patients with COVID-19 there are cases of secondary infection by some bacteria concomitantly, for this reason, the use of antimicrobials, mainly macrolides, was included as prophylaxis in the protocol of some cities (Oliveira et al., 2020).

Among the main variants of SARS-CoV-2, one has presented an imminent risk in Brazil and in other countries, the Delta variant (B.1.617.2), due to its greater transmissibility, leading to a worsening of the pandemic picture. The emergence of variants is a matter of global concern, as they are considered serious threats to public health, as currently available vaccines may have limits in terms of effectively blocking virus transmission (Planas et al., 2021; Yadav et al., 2021).

The present study is a literature review based on journal articles with the aim of clarifying and presenting discussions about the COVID-19 disease, its variants and prevention measures, as well as conducting a narrative about a possible health crisis, arising from the excessive use of antimicrobials, causing an increase in the profile of bacterial resistance, which already occurs and can be aggravated by the pandemic.

2. Methodology

The present study is characterized as a quantitative explanatory literature review. This type of research is considered to be that which seeks to identify explanations and their relations with the phenomenon studied (Gil, 2017).

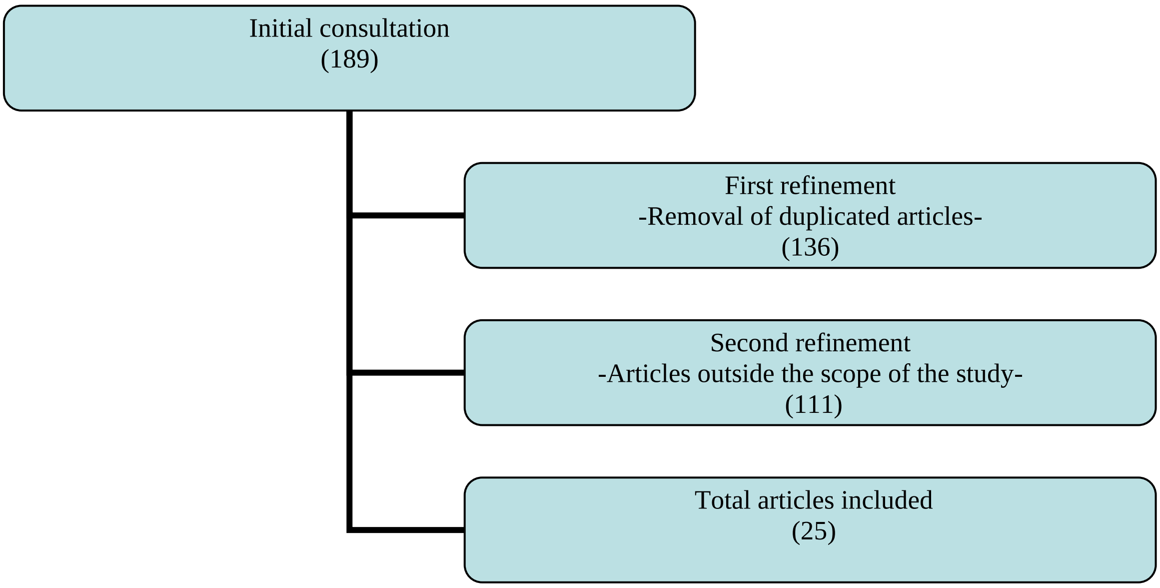
To this end, a literature review was conducted on bacterial resistance due to the indiscriminate use of antimicrobials and the possible impacts caused by the pandemic of COVID-19, as well as the variants of worldwide concern. Such research was conducted between the months of august and september 2021, as the purpose of mapping the scientific production on the referred theme in the period comprising the years 2019 to 2021.

Data collection was based on the Scientific Electronic Library Online - SCIELO, National Library of Medicine - PubMed, CAPES Journal Portal, Google Scholar, National Agency for Sanitary Surveillance (ANVISA) and the Centers for Disease Control and Prevention (CDC). Books that are reference in the subject discussed were also used.

We used papers that presented in their body the following descriptors: "irrational use of antimicrobials"; "bacterial resistance"; "pandemic"; "variants" and "COVID-19".

In this initial consultation a total of 189 articles were found, and then two stages of refinement were performed. In the first, we chose to remove the duplicate articles, and in the second, we chose to exclude those that were not within the scope of the intended study, leaving a total of 25 articles. For the refinement of article selection, the procedure indicated in Flowchart 1 was adopted.

Flowchart 1 - Article selection procedure.



Source: Authors.

3. The Coronavirus

Coronavirus is characterized by a zoonotic virus, an RNA virus of the order Nidovirales, of the Coronaviridae family. This is a family of viruses that cause respiratory infections, which were first isolated in 1937 and described as such in 1965 because of their microscopic profile resembling a crown. The types of coronaviruses known to date are: alpha coronavirus HCoV-229E and alpha coronavirus HCoV-NL63, beta coronavirus HCoV-OC43 and beta coronavirus HCoV-HKU1, SARS-CoV (causing severe acute respiratory syndrome or SARS), MERS-CoV (causer of Middle East respiratory syndrome or MERS) and SARS-CoV-2, a new coronavirus described in late 2019 after reported cases in China (Lima, 2020).

Since then, several variants have emerged in several countries around the world, such as the United Kingdom, South Africa, Brazil and India, thus modifying the dynamics of transmissibility and potential immune flight from the disease. Such variants were classified by WHO as variants of concern (VOC) and variants of interest (VOI), after convention of the WHO Working Group on the Evolution of SARS-CoV-2 (PAHO, 2021; Yadav et al., 2021).

Among the variants of concern are Alpha (B.1.1.7), first described in the UK; Beta (B.1.351), initially described in South Africa; Delta (B.1.617.2), reported in India and GAMA variant (B.1.1.28.1), also known as the former P1 first described in Brazil, both in 2020. Among the variants of interest (VOI) are the Eta (B.1.525), described in countries such as the United Kingdom and Nigeria; Iota (B.1.526), reported in the United States of America; Kappa (B.1.617.1), initially described in India and Lambda (C.37), described in Peru, both in 2020. The Centers for Disease Control and Prevention (CDC) has a third classification for the variants, thus differing of the WHO, defined as high consequence variant (VOHC), such differentiation occurs because the importance of the variants may vary according to location, however there is no report on it (Abdool Karim & de Oliveira, 2021; CDC, 2021; PAHO, 2021).

3.1 SARS-CoV-2 Delta variant (B.1.617.2)

The B.1.617 lineage, originating in India, has spread to many countries such as the United Kingdom and Brazil, causing it to evolve into three sub-lines: B.1.617.1 (Kappa), B.1.617. 2 (Delta) and B.1.617.3. Likewise, in the other variants, there are mutations in the region of the genome responsible for the orientation and production of the Spike protein (S), present on the surface of the virus, in the Delta variant. Viral protein modification benefits the virus through the adaptation mechanism. Such a Protein S mutation increases adherence to host cell receptors and promotes a reduction in the action of antibodies (Abdool Karim & de Oliveira, 2021; OPAS, 2021).

The Delta variant has been shown to be a greater public health threat than other variants due to its increased transmissibility. It is estimated that the risk of hospital admission for COVID-19 is doubled in individuals with the Delta variant compared to the Alpha variant. Prior to the Delta variant, Brazil had already been the target of the Alpha variant, in Amazonas, alerting health authorities due to changes in certain patterns such as: mortality by COVID-19, age group, sex, pathogenicity profile and virulence. There is a need for constant scientific improvement in the health surveillance system, coming from the virology and genomics sector, so that new mutations can be prevented, mainly through herd immunization. Because, knowing the pathogenicity of the variant, preventive measures can be taken, preventing its spread. Social distancing, mask use, constant hand washing, hand hygiene and 70% alcohol surfaces, among others, are still recommended (CDC, 2021; PAHO, 2021).

A recent study in the United Kingdom estimated that the effectiveness of vaccines is reduced against the newer variants, when compared to the original strain of coronavirus, especially with just one dose of it. Therefore, this finding reinforces efforts to expand vaccine coverage in two doses (Abdool Karim & de Oliveira, 2021; Frampton et al., 2021; PAHO, 2021).

3.2 Antimicrobial Drugs used to treat COVID-19

COVID-19 is a disease caused by acute respiratory syndrome 2 (SARS-CoV-2), and since December 2019, it has affected the world (Chen & Li, 2020). It has a clinical spectrum ranging from asymptomatic to severe infections. Although this is considered a virus in clinical medicine, it is observed that it has had some cases of secondary infection by some bacteria in concurrency, for this reason, the use of antimicrobials, especially macrolides, as prophylaxis (Vellano & Paiva, 2020). However, with this conduct of use of antimicrobials as prophylaxis for all patients, that is, even for those without a diagnosis of clinical confirmation tests for COVID-19 infection, a scenario that was already threatened, that of bacterial resistance, can start.

Bacterial resistance can be classified as intrinsic and acquired, thus, the intrinsic form is understood as the naturally inherited resistance genetically, while the acquired one comes from external factors, such as the irrational use of antimicrobials (M. Oliveira et al., 2020). Thus, bacterial resistance results in the bacterium's capacity to adapt, and when this is related to antimicrobials, it occurs when the bacterium expresses genes that encode the biochemical mechanism by inhibiting the production of enzymes that end up inactivating drugs, the alteration of action targets and alteration of the permeability of the outer membrane or efflux thereof (AR Teixeira et al., 2019).

The misuse and excessive use of antimicrobials favors the emergence of superbacteria, which are subdivided into extensively resistant, when the bacteria occurs in one or two classes; multidrug-resistant, when resistance occurs in an antimicrobial of three or more classes; or even in pan-resistant, when resistance occurs in all classes of antimicrobials (M. Oliveira et al., 2020).

Azithromycin (macrolide) is one of the drugs widely used in the early treatment of patients with COVID-19, with the aim of preventing or treating a possible secondary infection (pneumonia), as well as clarithromycin, among others. However, the etiology of the disease must be considered, if it is not of bacterial origin, there is no apparent reason for prescribing this drug (Paumgartten & Oliveira, 2020). According to Oliveira, Pereira and Zamberlam (2020), and according to the WHO, there is growing concern about the indiscriminate use of antimicrobials in the COVID-19 pandemic scenario. The Pan American Health Organization (PAHO) considers that antimicrobial resistance is equally dangerous when compared to the pandemic and that centuries of studies and medical progress could be destroyed if significant measures are not adopted regarding its rational use (PAHO, 2020).

Monitoring the use of antimicrobials in the region of the Americas, both in human and animal health, still requires special attention, although some countries in this region, such as Brazil, have contributed relevant information on antimicrobial sales to the WHO Report on Use Surveillance of Antimicrobials, however, such monitoring still needs to be expanded. PAHO supports in different sectors the fight against antimicrobial resistance, as well as its early detection and coordinated response against pathogens. It also supports the research, development and dissemination of scientific results, and alerts countries to act cooperatively, thus increasing public awareness on this issue (J.B. da Silva et al., 2020).

It is important to emphasize that this issue can have devastating consequences, ranging from sanitary crises to diseases that are already under control or emerging, as is the case with COVID-19. In addition to representing a public economic problem, another factor to be considered is that the pharmaceutical industries have not invested in research and development for the production of new antimicrobials, as they demand high expenses over a long period of time (MO da Silva & Aquino, 2018).

3.3 The problem of using antimicrobials in patients positive or not for COVID-19

It is believed that a possible way to try to minimize the problem of the use of antimicrobials in patients with COVID-19 would be to test the patient, who has already been positive for this disease, to verify if he actually has a secondary bacterial infection, requesting a test blood culture and/or antibiogram, in order to prescribe the antimicrobial and enable the appropriate therapy (Oliveira Junior, 2016). Such sensitivity tests are exams analyzed by microbiology laboratory professionals, easy to perform, low cost and high reliability, being commonly used in the development of therapeutic guides, with indication for any microorganism that causes an infectious process that requires the use of these drugs (ANVISA, 2017).

Thus, it would minimize the problem of putting the use of antimicrobials as a protocol for all patients. Otherwise there may be a critical situation related to its resistance, and also some undesirable adverse effects in patients due to the use of these drugs. Interactions between macrolides and other widely used medications are observed, such as: oral contraceptives, methylprednizone, digoxin, and some benzodiazepines, midazolam, warfarin. In addition, azithromycin should be avoided, or used with caution, in patients with severe renal or liver failure (Oliveira Junior, 2016; Paumgartten & Oliveira, 2020).

4. Final Considerations

Through these considerations, it can be concluded that COVID-19 is a disease caused by the acute respiratory syndrome (SARS-CoV-2) and has affected the whole world. It has a clinical spectrum ranging from asymptomatic to severe infections. Several variants have emerged in several countries, thus modifying the dynamics of transmissibility and potential immune flight from the disease. Currently, the Delta variant proves to be a greater threat to public health because of its increased transmissibility and that preventive measures must be taken to prevent its spread.

The misuse and excessive use of antimicrobials favors the emergence of superbugs and such resistance is a global problem and can be even more aggravated in our parents, due to their irrational use. Its rational use thus avoids major sanitary crises, until the achievement of better advances in the development of new drugs in this class of medications, which are already so outdated and without new therapeutic options. With the help of laboratory and clinical tests, a therapeutic intervention must be carried out, observing the best options for each clinical case, since COVID-19 is a new disease and still under study.

It is expected that, with the development of new therapies and current vaccines, clinical protocols for this disease will be better developed, until reaching its total eradication.

Finally, based on the literature presented, it is suggested that future work should include further clinical studies on the subject in question, since it is believed that such a procedure would bring a broad contribution to health promotion, public health, and scientific research.

Acknowledgments

The authors are grateful to the development agencies in Brazil, Coordination for the Improvement of Higher Education Personnel - CAPES Foundation (Ministry of Education of Brazil, Brasília - DF), Foundation for Research Support of Minas Gerais (Fundação FAPEMIG, Brazil) and the National Council Scientific and Technological Development (CNPq, Brazil). Luiz, L.C thanks the CAPES Foundation for the postdoctoral scholarship. Silva, D.D.M thanks the Federal University of Juiz de Fora (UFJF) for the master's scholarship.

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